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the following comments relative to the outstanding rejections as they may apply to the present claims is respectfully requested. Appendix A is a copy of the current claims and is attached for the Examiner's convenience. Favorable consideration of the following comments relative to the outstanding rejections as they may apply to the present claims is respectfully requested for the following reasons.

Information Disclosure

Applicants appreciate the Examiner's attention to the previously filed Information Disclosure Statement. Of note, the priority date of WO0048000A1 is August 2000; the filing date for the present invention is October 6, 1997. Applicants note that WO0048000A1 is not prior art. Nevertheless, a copy of WO0048000A1 is included with this response for the Examiner's convenience. In addition, the Information Disclosure Statement has been corrected to comply with 37 CFR 1.98(a)(2). A copy of each U.S. and foreign patent and publication is now in the file. Applicants request that the information therein be considered.

Response to Rejections under 35 USC § 102

Claims 39, 40, 43-45, 47 and 48 are rejected under 35 USC § 102(e) as being anticipated by Pinkel *et al.* (US005690894A). Examiner argues that the Pinkel patent teaches an assay method corresponding to the disclosed apparatus (Fig. 4) which comprises a sensor array 14 having at least two subpopulations (the groups of strands 10) of different sensor elements." The Examiner further states that the assay method disclosed in Pinkel comprises "measuring first fluorescent signals (column 13, lines 33-39) of at least two of the sensor elements 11 of the first subpopulation (group) with detector 20, and summing the first fluorescent signals (column 9, lines 12-14 and 21-25)." Applicants respectfully traverse.

Pinkel discloses the fabrication and use of biosensors comprising a plurality of optical fibers where each fiber has biological "binding partners" attached to its "sensor end." In column 8, lines 50-67 and column 9, lines 12-14 and 21-25 (the sections referred to by the

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Examiner) disclose alternative ways of measuring the signal generated by the biosensor, which are "each optical fiber or group of fibers may bear a multiplicity of biological binding partners as long as that multiplicity differs from the biological binding partners of multiplicity of biological binding partners present on other fibers or groups of fibers comprising the optical fiber array 14. The fibers bearing like species of binding partner may be physically grouped together thereby producing distinct regions of the sensor face 13..." and "to measure the aggregate signal provided by the entire transmission face 15 of the biosensor" or "to read the signal from single optical fibers 10 or from groups of optical fibers where all of the optical fibers 10 in a group bear the same species of biological binding partner." That is to say, the composition takes a single reading of either a single fiber or a group of fibers.

In contrast the present invention claims a method providing for a sensor array comprising a first and second subpopulations comprising first and second sensor elements, respectively, adding a sample comprising a first target analyte that binds to the first sensor elements, then measuring the first fluorescent signal of the sensor elements, and summing the first and second fluorescent signals.

The law is well established that in order to anticipate a claim, the prior art must disclose "each and every element" of the claimed invention. SSIH Equipment S.A.v. U.S. Inc. Int'l. Trade Commission, 218 USPQ 678, 688 (Fed. Cir. 1983). As stated by the Federal Circuit in In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990), "[f]or a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference." (Emphasis added). See also Glaverbel Societe Anonyme v. Northlake Marketing & Supply, Inc., 33 USPQ2d 1496 (Fed. Cir. 1995).

Here, each and every element is not present, since nowhere in the Pinkel patent is measuring and summing individual signals from individual sensor elements of a subpopulation mentioned. Accordingly, the reference does not anticipate the present claims, and the rejection is improper. With specific reference to claim 40, Pinkel does not teach adding a sample comprising a second target analyte that bind to the second sensor elements, then measuring a third fluorescent signal of a first of the second sensor elements, and

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measuring a fourth fluorescent signal of a second of the second sensor elements, and summing the third and fourth fluorescent signals.

Response to Rejections under 35 USC § 103

Applicants note that, as stated in MPEP § 2143.03, "[i]f an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is non-obvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)." Hence, it is logically and legally impossible for claims 41 and 42 to be obvious, because the independent claim from which they depend is nonobvious. Nevertheless, assuming *arguendo* that claims 46, 41 and 42 could be obvious even though the independent claim from which they depend is nonobvious, Applicants submit that Examiner does not make a *prima facie* case for obviousness with regard to claims 46, 41 and 42.

Claim 46 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Pinkel *et al.* (US005690894A). Examiner argues that it would have been obvious to one of ordinary skill in the art to adjust the baseline of fluorescence signals in the method of Pinkel because the detector system may be employed with a computerized data acquisition system and analytical program (columns 12, lines 10-22) and such an adjustment is a known and useful step in accurately measuring responses.

Claims 41 and 42 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Pinkel *et al.* (US005690894A) in view of Lough *et al.* (US005900481A). The Examiner states that "[t]he beads of Lough *et al.* are suitable for the types of binding molecules used and fluorescent signals measured in the sensor array 14 of Pinkel *et al.* and further provide the convex surface Pinkel *et al.* identifies as advantageous." The Examiner further states that "it would have been obvious to one of ordinary skill in the art at the time of the invention was made to modify the method of Pinkel *et al.* to specify that the sensor ends therein were bound to beads as suggested by Lough *et al.* (as the fiber strands 10 in Pinkel *et al.*, qualify as a support as described by Lough *et al.* at column 3, line 29)." Applicants respectfully traverse.

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Pinkel was described above; and is directed to the fabrication and use of biosensors comprising a plurality of optical fibers each fiber having attached to its "sensor end" biological "binding partners," but it does not disclose a method of measuring and summing individual signals from single optical fibers within a group.

Lough *et al.* teaches compositions comprised of at least one bead conjugated to a solid support and further conjugated to at least one nucleic acid and methods for making such compositions.

Applicants note that there are three requirements to establish a *prima facie* case of obviousness. These include that "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." (MPEP § 2143). Applicants note that a rejection under § 103 based on a single prior art reference must be supported by some suggestion of the claimed invention or motivation to reach the claimed invention which is found in that single prior art reference. *In re Laskowski*, 10 USPQ2d 1397 (CAFC 1989).

With regard to claim 46, the Examiner is reminded that "the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. MPEP §2143.01.

With regard to claims 41 and 42, in *Dow Chemical Co. v. American Cyanamid Co.*, 2 USPQ2d 1350 (CAFC 1987), the Federal Circuit affirmed a district court holding that various patents were not invalid as obvious over a prior art reference because the prior art reference "taught away" from the inventions in those patents.

The prior art teaches away from combining the beads of Lough with the surface of Pinkel. Pinkel teaches an advantageous convex surface "glass fiber filter." The beads of Lough would roll off the convex surface of the fiber end. Even assuming *arguendo* that the convex surface of Pinkel was a suitable surface for the beads of Lough, Pinkel teaches that a convex end is in and of itself suitable for binding molecules; hence, there is no motivation to combine the beads of Lough with Pinkel.

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Hence, a *prima facie* case of obviousness has not been made against claims 46, 41 and 42. Accordingly Applicants respectfully request Examiner to withdraw his rejection.

Response to Submissions

The Examiner claims that Applicant's contention that a detector arranged to read the signal from groups of optical fibers 10 where all of the optical fibers 10 in a group bear the same species of biological binding partner will then individually evaluate the signal from each fiber in that group is unpersuasive. The Examiner argues that evaluation is performed at a level of the biological binding partner in the aggregate and the contribution of the individual fibers to the group signal is a summation since there is no preservation of a fixed spatial relationship between any of the transmission ends 12 in a group of optical fibers bearing a particular biological partner... a CCD element or phototube is used to detect a signal representing the binding of the particular partner regardless of which fiber it bound to. The Examiner argues, with regard to the the technical difficulty in measuring individual signals from individual optical fibers in a group, that the disclosure of Pinkel is adequate to measure individual signals from individual optical fibers 10, because "in the extreme case the signal for each optical fiber comprising the optical fiber array 14 can be individually focused." And therefore, the presence of the fibers in a group is no barrier to those skilled in the art using the disclosure of Pinkel to measure individual signals from individual optical fibers in a group, column 11, lines 61-63.

The test under § 103 is not whether an improvement or a use set forth in a patent would have been obvious or nonobvious. The test is whether the claimed invention, considered as a whole, would have been obvious or nonobvious. *Jones v. Hardy*, 220 USPQ 1020, 1025 (CAFC 1984). Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness. *The Gillette Co. v. S.C. Johnson & Son*, 16 USPQ2d 1923, 1927 (CAFC 1990).

Here, the Examiner did not look at the invention as a whole. When summarizing the disclosure of the prior art, Pinkel states: "Thus the detector is preferably arranged to read the

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signal from single optical fibers 10 or from groups of optical fibers where all of the optical fibers 10 in a group bear the same species of biological binding partner. The individually focused fibers are referring to a single biological binding partner. The present invention requires two subpopulations as well as measuring and summing the fluorescent signals of two sensor elements.

The *prima facie* obviousness elements have not been met. Hence, the determination of obviousness should be withdrawn.

CONCLUSION

Applicants respectfully submit that the application is now in condition for allowance and an early notification of such is solicited. If, upon review, the Examiner feels there are additional outstanding issues, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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Appendix A

PENDING CLAIMS

39. An assay method comprising:

- a) providing a sensor array comprising:
 - i) a first subpopulation comprising first sensor elements; and
 - ii) a second subpopulation comprising second sensor elements;
- b) adding a sample comprising a first target analyte that binds to said first sensor elements;
- c) measuring
 - i) a first fluorescent signal of a first of said first sensor elements; and
 - ii) a second fluorescent signal of a second of said first sensor elements; and
- d) summing said first and second fluorescent signals.

40. A method according to claim 39 further comprising:

- b) adding a sample comprising a second target analyte that binds to said second sensor elements;
- c) measuring
 - i) a third fluorescent signal of a first of said second sensor elements; and
 - ii) a fourth fluorescent signal of a second of said second sensor elements; and
- d) summing said third and fourth fluorescent signals.

41. A method according to claim 39 wherein said first and second sensor elements comprise beads.

42. A method according to claim 39 wherein said sensor array comprises beads distributed in wells.

43. A method according to claim 39 wherein said first and second sensor elements comprise

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chemical functional groups.

44. A method according to claim 39 wherein said first and second sensor elements comprise oligonucleotides.

45. A method according to claim 39 wherein said first target analyte is an oligonucleotide.

46. A method according to claim 39 wherein prior to said summing, the baseline of said first and second fluorescent signals are adjusted.

47. A method according to claim 39 wherein the signal-to-noise ratio is increased as a result of said summing.

48. A method according to claim 39 wherein said sensor array comprises a fiber optic bundle.